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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,134	10/20/2002	Chandrasekhar Satishchandran	AM100013	5538

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
09/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/009,134	SATISHCHANDRAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68-174* is/are pending in the application.

4a) Of the above claim(s) *68-106,169 and 170* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *107-168, 171-174* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 06/08/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 03/08/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 68-173 and new claim 174 are pending. Claims 107-168 and 171-174 are currently under examination. Claims 68-106 and 169-170 are withdrawn as being drawn to a non-elected invention.

Priority

Claim 139 is accorded a priority date of 04/19/2000.

New Claim Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 174 is rejected under 35 U.S.C. 103(a) as being unpatentable over Werther et al. (cited on PTO Form 892 filed 08/07/2006), Fire et al. (cited on PTO Form 892 filed 08/07/2006), Heifetz et al (cited on PTO Form 892 filed 08/07/2006), Calabretta et al. (US Patent No. 5,734,039) and Thompson et al. (cited on PTO Form 892 filed 08/07/2006).

The instant claim is drawn to an expression vector for reducing or inhibiting the function of at least one target gene in a mammalian cell wherein the expression vector encodes two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of at least one target gene, wherein the vector encodes tow or more different RNA molecules that are less than about 750 nucleotides in length and each comprising at least 11 to 30 nucleotides are involved in the double stranded RNA molecule.

Werther et al. teach a multivalent antisense molecule targeted to two sequences of a target gene IGFBP or targeted to two or more sequences in different target genes such as IGFBP-2 and IGFBP-3 (see column 3). Werther et al. does not each a partially double stranded RNA comprising two or more different double stranded RNA sequence that are complementary to two or more sequence of at least one target gene. Werther et al. does not teach expression of said double stranded RNA from an expression vector wherein said expression vector expresses two different double stranded RNA sequences using two promoters.

Calabretta et al. teach a multivalent antisense molecule targeted to two sequences of cooperating oncogenes and teach vectors for expression of each said antisense molecules under the control of a corresponding first and second promoter for efficient endogenous expression of multiple antisense sequences in cells (see column 19, lines 50-63).

Fire et al. teach double stranded RNA wherein the duplex regions of the RNA are capable of hybridizing with the target gene wherein the length of the duplex regions are from 25 to 400 bases (see columns 7-8). Fire et al. teach expression vectors comprising T7 polymerase promoters and teach the target gene may be derived from any cell of any organism wherein the organism may be a plant, animal or human (see column 8, lines 12-20). Fire et al. additionally teach the target gene may derived from any pathogen or any cell already infected by a pathogen such as HIV for example (see column 10, lines 8-18). Fire et al. teach the use of double stranded RNA for RNA inference is an effective alternative to antisense methodologies.

Heifetz et al. teach production of a double stranded interfering RNA comprising introducing into plant cells DNA sequences encoding a sense RNA strand and an antisense RNA strand into an expression vector wherein the sense and antisense RNA strands are complementary to each other and form a double stranded RNA (see page 8). Heifetz et al. teach the complementary regions can be 15, 50 or 500 nucleotides in length (see page 11). Heifetz et al. teach the DNA sequences are preferably operably linked to one or more promoters each expressing a sense or antisense RNA wherein the promoter is a heterologous promoter (see page 10 last paragraph to the top of page

11). Heifetz et al. teach the DNA sequences that form the double stranded RNA are inserted into the same vector wherein the sequences encodes a sense and an antisense strand or the DNA sequences that encode a sense strand or an antisense strand are in separate vectors (see pages 8-9). Heifetz et al. teach viral vectors can be used to introduce the DNA molecules into the plant cells (see page 11) and further teach methods of altering the expression of a target gene by introducing a vector comprising said DNA sequences as stated above (see pages 12-13 and Examples 1 and 3).

It would have been obvious to one of skill in the art to make a multitargeted double stranded RNA wherein said double stranded RNA targets at least one or more than one target gene and further it would have been obvious to use expression vectors comprising two promoters for expressing said dsRNAs.

One would have been motivated to make a multitargeted double stranded RNA targeted to two or more sequences of at least one target gene because certain target sequences are capable of mutation and targeting multiple sites on a target gene is advantages for effective therapeutics. Further, one would have been motivated because certain diseases are triggered by expression from similar genes and therefore inhibition of multiple genes, as taught by Werther et al. is an effective method. Additionally, Calabretta et al. teach simultaneous targeting of genes using two antisense compounds is advantageous to inhibit expression of cooperating oncogenes responsible for cancer and therefore the skilled artisan would have clearly been motivated to express dsRNA using different promoter for efficient expression of each

dsRNA targeted to a target gene for the purpose of inhibiting gene expression. One would have been motivated to use double stranded RNA because Fire et al. teach double stranded RNA capable of initiating RNA interference is more sequence specific alternative to reducing expression of a target gene than antisense type mechanisms (see columns 1-3). One would have had a reasonable expectation of success given that Werther et al. teach construction of multitarget antisense and Fire et al. and Heifetz et al. teach gene inhibition using double stranded RNA wherein said duplex region is complementary to said target gene and wherein said double stranded RNA is expressed using an expression vector comprising one or more promoters. Further one would have expected success given Heifetz specifically teach construction of a single vector capable of expressing sense and antisense sequence of a dsRNA from two promoters (see page 10, Example F on page 26 and claim 11).

Thus, in absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Arguments

Re: Claim Rejections - 35 USC § 102

The rejection of record of claim 139 under 35 U.S.C. 102(a) as being anticipated by Leirdal et al. (cited on PTO Form 892 filed 08/07/2006) in the Office action mailed 03/08/2007 is withdrawn in response to claim amendments filed 06/08/2007.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 107-168 and 171-173 under 35 U.S.C. 103(a) as being unpatentable over Werther et al. (cited on PTO Form 892 filed 08/07/2006), Fire et al. (cited on PTO Form 892 filed 08/07/2006), Heifetz et al (cited on PTO Form 892 filed 08/07/2006), Calabretta et al. (US Patent No. 5,734,039) and Thompson et al. (cited on PTO Form 892 filed 08/07/2006) is maintained for the reasons of record in the Office action mailed 03/08/2007.

Applicant's arguments filed 06/08/2007 have been fully considered but they are not persuasive. Applicants argue the skilled artisan would not have been motivate to combine the teachings of Werther et al. and Fire et al. to produce a multitarget double stranded RNA as claimed because at the time of the instant invention, long double stranded RNA cause an interferon stress response when introduced into mammalian cells, which is not seen with the antisense construct proposed by Werther et al. Applicants argue at the time of the present invention, the tendency was to use shorter dsRNA and not longer molecules as instantly claimed. This argument is not convincing.

Fire et al. specifically teach a process for silencing target gene expression using a partial or fully double stranded RNA, therefore one would have been motivated to use these double stranded RNA to construct a multivalent molecule to silence gene expression. Moreover, at the time of the invention it was known that long double stranded molecules could effectively silence gene expression because such molecules were cleaved into shorter dsRNA once inside the cell with a dicer molecule, therefore

there was a reasonable expectation of success that long dsRNA molecules could effectively silence target gene expression. Furthermore, Heifetz et al. teach the use of dsRNA of 15 and 50 that can be effectively used to silence target gene expression. Therefore, one of skill in the art would have clearly been motivated to use the dsRNA taught by Fire et al. and Heifetz et al. to construct a multitargeted dsRNA to silence target gene expression.

Applicants further argue that at the time of the instant invention one of skill in the art would not have been motivated to expressed more than one dsRNA from separate promoters on the same vector because it was well known that competitive interference between promoters on a single vector results in preferential expression of one gene over the other. The argument is not convincing.

As noted by applicant, Calabretta teach expression of two different antisense sequences from a single vector construct using separate promoters for efficient endogenous expression of multiple antisense sequences in cells. Although Calabretta does not teach a specific embodiment comprising construction of said construct, one of skill in the art would have been motivated to use the teachings of Calabretta et al. to construct a construct expressing different dsRNA to target multiple genes given Calabretta et al. teach simultaneous targeting of genes using two antisense compounds is advantageous to inhibit expression of cooperating proteins responsible for certain diseases. Moreover, not only would one of skill in the art been motivated to make a single vector comprising two promoters capable of expressing different dsRNA from said single vector, one would have expected success given Heifetz specifically teach

construction of a single vector capable of expressing sense and antisense sequence of a dsRNA from two promoters (see page 10, Example F on page 26 and claim 11). Therefore, the teachings of Calabretta et al. combined with the teachings of Heifetz et al. provide motivation to construct a single vector capable of expressing dsRNA from different promoters to target and silence expression from different target genes.

Thus, in absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-

3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong
Examiner
Art Unit 1635

/Sean McGarry/
Primary Examiner
AU 1635